1. Scientific Abstract

Many malignancies are associated with somatic mutations in p53. Quantities of abnormal p53 protein are often markedly increased in tumor cells as a consequence of such mutations, and several studies have shown that cytotoxic T cells that recognize non-mutant epitopes in p53 can selectively kill malignant cells, but not normal cells. Therefore non-mutant p53 may be a reasonable shared antigen for tumor selective immunotherapy. One immunotherapeutic strategy that is being developed by numerous investigators is to use dendritic cells (DC's), which are potent antigen presenting cells, "loaded" with target tumor antigens. One method of "loading" DC's with target antigens is to use an adenoviral vector that contains the gene coding for the target antigen. It has been shown that DC's can be transduced with recombinant adenoviral vectors and effectively present the protein encoded by the transgene carried by the adenoviral vector, and that this does not decrease DC function or viability.

This is a phase I/II study involving patients with extensive-stage small cell lung cancer (SCLC), who will be treated initially with conventional chemotherapy to reduce the bulk of their disease, and then subsequently immunized with a vaccine consisting of DC's transduced with the wild type p53 gene using an adenoviral vector (Ad-p53 DC). SCLC has an extremely poor prognosis despite frequent initial responses to chemotherapy. Furthermore, mutations in p53 occur in approximately 90% of patients with SCLC, and of these, about 90% overexpress mutant p53 protein. This makes these patients suitable for the testing of the clinical efficacy of the Ad-p53 DC vaccine. Peripheral blood mononuclear cells will be harvested from patients prior to the administration of chemotherapy and stored frozen. The patients will receive standard first line chemotherapy, which will result in a significant clinical response in 80-90% of the patients. After the chemotherapy has been completed, the stored peripheral blood mononuclear cells will be thawed, and cultured in the presence of IL-4 and GM-CSF to produce DC's. These DC's will then be transduced with Ad-p53. The patients will be immunized with the Ad-p53 DC vaccine every other week on days 1, 14, and 28. If the restaging studies show no progression of disease then the patients will receive 3 more vaccine injections monthly on days 56, 84, and 112. Patients will be monitored for evidence of toxicity, the development of a specific immune response, and objective tumor responses. The maximum tolerated dose will be determined in the phase I portion of this study, where the dose of the vaccine will be escalated in 3 cohorts of patients, and then a total of 40 patients will be treated with the MTD in the phase II portion of the study.